Licofelone Merckle

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EuroAlliance (a consortium of Alfa Wassermann SpA, Lacer SA and Merckle GmbH) is developing licofelone, a dual cyclooxygenase and 5-lipoxygenase inhibitor for the potential treatment of inflammatory disorders including osteoarthritis.

Originator Merckle GmbH

Licensees Alfa Wassermann SpA, Lacer SA

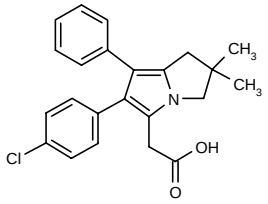
Status Phase III Clinical

Indications Inflammation, Osteoarthritis, Pain

Actions 5-Lipoxygenase inhibitor, Analgesic, Cyclo-oxygenase inhibitor, Non-steroidal anti-inflammatory

Synonym ML-3000

CAS *1H*-Pyrrolizine-5-acetic acid, 6-(4-chlorophenyl)-2,3-dihydro-2,2-dimethyl-7-phenyl-
Registry No: 156897-06-2



Introduction

Blocking the cyclooxygenase (COX) pathway of arachidonic acid (AC) metabolism by conventional non-steroidal anti-inflammatory drugs (NSAIDs) not only results in decreased production of gastroprotective prostaglandins (PGs) but also in the increased metabolism of AC via the 5-lipoxygenase (5-LOX) route. This 'shunting effect' leads to increased production of leukotrienes (LTs), which contribute to inflammatory processes and further gastrointestinal (GI) damage. Thus, developing dual COX/5-LOX inhibitors may enhance anti-inflammatory effects and reduce the undesirable side effects associated with NSAIDs, especially those in the GI tract [472612].

Licofelone is the most promising of the dual COX/5-LOX inhibitors discovered by Merckle GmbH and is being developed by EuroAlliance (a consortium of Alfa Wassermann SpA, Lacer SA and Merckle). Pharmacological studies have demonstrated that the drug has analgesic, antipyretic, anti-inflammatory and significant anti-asthmatic activity without causing GI damage. It is currently in a phase III trial for the treatment of osteoarthritis (OA) [280077], [361142], [454683].

Synthesis and SAR

Initial synthesis of licofelone proceeded with poor overall yield (< 5%) [159855]. Cossy and Belotti reported a short and efficient synthesis of licofelone that featured a thermal-acid-promoted bicyclization of an ω-acetylenic amino ester [276312]. Basic phase-transfer catalysis of 1-chloro-3-phenyl-2-propyne with isobutyraldehyde in the presence of NaI produced an aldehyde. This aldehyde was condensed with methyl glycinate hydrochloride under reductive amination conditions to yield an ω-acetylenic amino ester, which was heated at 150°C in the presence of 1 equivalent of pivalic acid to give tetrahydro-6-oxo-1*H*-pyrrolizine. Acylation with diethyl oxalate under basic conditions introduced a carboxylic acid side chain. The resulting β-diketone was entirely enolized. A Suzuki cross-coupling reaction was used to introduce the 4-chlorophenyl group. Treatment with *N*-phenyltrifluoromethanesulfonimide produced a triflate. This was coupled with (4-chlorophenyl)boronic acid in the presence of $Pd(PPh_3)_4$ and Na_2CO_3/H_2O in refluxing tetrahydrofuran. The ethyl ester of licofelone was produced by deoxygenation via the 4-toluenesulfonylhydrazone, which after saponification led to licofelone at an overall yield of 19% [276312].

From a series of 6,7-diaryldihydropyrrolizin-5-yl acetic acids, licofelone, with its 4-chloro substituent, was the most potent and well-balanced dual inhibitor of both COX and 5-LOX [159855].

Pharmacology

The inhibition of COX and 5-LOX by licofelone was first determined in a bovine thrombocyte intact cell assay and intact bovine polymorphonuclear leukocytes, respectively (IC_{50} values of 0.21 μM for COX and 0.18 μM for 5-LOX) [159855]. In a human whole blood assay, licofelone (0.3, 1.0, 3.0, 10 and 30 μg/ml) and indomethacin (0.3, 1.0, 3.0, 10 and 30 μg/ml) concentration-dependently inhibited the synthesis of PGE_2 (IC_{50} = 3.9 and 4.5 μM, respectively). In contrast to licofelone, indomethacin produced an increase in LTC_4 of up to 155.5% of control. Furthermore, licofelone (1 to 10 μM) inhibited the synthesis of LTB_4 in a concentration-related manner (IC_{50} = 3.6 μM) in a basophilic leukemia cell assay using RBL-1 cells [472600]. Licofelone inhibited LTC_4 formation by mixed polymorphonuclear leukocyte/platelet suspensions stimulated with A-23187 (IC_{50} = 3.8 μM). Licofelone also inhibited the generation of reactive oxygen species, release of elastase by polymorphonuclear

leukocytes, and homotypic polymorphonuclear leukocyte aggregation induced by *N*-formyl-methionyl-leucyl-phenyl-alanine (fMLP), complement fraction 5a (C5A) and platelet activating factor (PAF), respectively [472601]. These *in vitro* studies demonstrated that licofelone inhibits 5-LOX as well as COX-1 and COX-2 activity, and therefore, polymorpho-nuclear leukocyte responses relevant to the pathogenesis of inflammation.

The pharmacodynamic profile of licofelone has been assessed and compared with widely used NSAIDs in various animal models. In a carrageenan-induced rat paw edema model, licofelone (10, 30 and 100 mg/kg) demonstrated an ED_{50} value of 17 mg/kg po and completely inhibited both PGE_2 and LTB_4 secretion, compared with indomethacin (10 mg/kg), which only inhibited secretion of PGE_2 [472618].

In a rat adjuvant arthritis model, groups of rats (n = 10) were orally dosed with either licofelone (10, 25 or 50 mg/kg) or with indomethacin (1 mg/kg bid). Decreases in secondary lesions in rats treated with licofelone (25 mg/kg) were similar to the decreases observed with indomethacin, indicating that the anti-inflammatory activity of licofelone is comparable to indomethacin [472618].

An oral dose of licofelone (10 mg/kg) was more effective than an oral dose of aspirin (50 mg/kg) in a mouse phenyl-quinone writhing model [472618]. The Randall and Selitto assay demonstrated that licofelone (30 mg/kg) was as effective as indomethacin (10 mg/kg) at increasing the pain threshold of inflamed paws in rats [472618].

In a brewer's yeast-induced hyperthermia model in rats, a significant antipyretic effect was noted with licofelone (10 mg/kg po), which lasted 3 h and was comparable to the effect of indomethacin (10 mg/kg po) [472618].

Licofelone was highly effective and potent in a guinea pig model of AC-induced bronchoconstriction (ED_{50} = 0.2 mg/kg iv) [472618]. In addition, licofelone (100 mg), administered as an aerosol to allergic sheep before antigen challenge, significantly inhibited the early bronchial response and completely blocked late antigen-induced broncho-constriction. It also attenuated airway hyper-responsiveness to aerosolized carbachol that occured 24 h after antigen challenge [326442].

In a rat laser-induced thrombus model, licofelone (10, 30 and 100 mg/kg po) demonstrated significant antithrombotic activity comparable to aspirin (30 and 100 mg/kg po). An *in vitro* study demonstrated that licofelone (1 to 100 µg/ml) had a marked platelet aggregation inhibiting effect [472602].

In a rat adjuvant arthritis model, licofelone (20 or 80 mg/kg/day bid for 28 days) significantly reduced the arthritis-associated deficiency of body growth, the edema/erythema score and splenomegaly. In the ankle joint, licofelone significantly reduced the overall histological score, synovial cell proliferation and bone/cartilage erosions, and also inhibited the appearance of fibroproliferative pannus [472610]. In the anterior cruciate ligament transection OA dog model, licofelone (2.5 and 5 mg/kg/day for 8 weeks) significantly decreased the size, grade and severity of cartilage lesions in the condyles and plateaus. It significantly decreased the level of PGE_2 in synovial fluid and LTB_4 production by synovium. Licofelone also markedly reduced the levels of collagenase 1 in cartilage and IL-1β in the synovial membrane [472608]. In another study using this model, licofelone (2.5 and 5 mg/kg/day for 8 weeks) markedly reduced the level of chondrocyte apoptosis, and significantly decreased the levels of caspase-3, COX-2 and iNOS in cartilage from both condyles and plateaus [472595]. *In vitro*, licofelone (0.8 to 8 µM) inhibited the production of PGE_2 and LTB_4 by OA osteoblasts at the highest dose, dose-dependently stimulated 1,25-dihydroxy vitamin D-induced alkaline phosphatase activity, and inhibited osteocalcin release via its effect on LTB_4 production [472594]. These results suggest that licofelone could be used as a disease-modifying drug for the treatment of OA and rheumatoid arthritis (RA).

The gastric-sparing properties of licofelone have also been investigated. The drug dose-dependently inhibited ATPase activity in pig gastric microsomes with an IC_{50} value of 16.6 µM. When the drug was diluted by 100-fold, the inhibitory effect was abolished. Licofelone-treated human gastric adenocarcinoma cells secreted less baseline and IL-1β-induced IL-8 with IC_{50} values of 0.82 and 1.2 µM, respectively [490628].

Metabolism

Plasma levels and distribution of radioactivity were examined using whole-body autoradiography after oral administration of ^{14}C-labeled licofelone (13.7 to 26.6 mg/kg) to female rats. Plasma levels of licofelone peaked at 3 to 4 h after administration, with a plasma $t_{1/2}$ of ~ 11 h. The highest tissue levels of licofelone were detected in the lung, liver, kidney, heart and intestine. Almost no penetration of the blood-brain barrier was noted; however, after 48 h there was a minor accumulation in fat. Of the total radioactivity, 58.3% was found in the feces and 7.9% in the urine [215072].

Licofelone (200 mg bid for 5 days and a single final dose of 200 mg on day 6) was administered in 18 healthy male and female young (mean age of 30.9 years) and elderly (mean age of 72.1 years) individuals. Following the first dose, mean C_{max} was similar for young (1665 ± 1151 ng/ml) and elderly (1637 ± 903 ng/ml) individuals. The maximum plasma concentrations were reached 0.74 to 4 h after administration, while the mean $AUC_{(0\ to\ 12)}$ was 23% lower in the young individuals (5646 ± 2073 versus 4582 ± 1927 ng.h/ml). Licofelone demonstrated similar C_{max} values in the two groups at steady-state, with young individuals having a C_{max} value of 1727 ± 829 ng/ml and elderly individuals having a C_{max} value of 1744 ± 616 ng/ml; the AUC was 20% higher in elderly individuals. $t_{1/2}(\beta)$ was greater in young individuals than elderly ones (11.1 ± 7.0 versus 8.7 ± 4.7 h), while the mean $t_{1/2}(\alpha)$ value was 15% higher in the elderly study population [477522]. No pharmacokinetic interaction between licofelone and warfarin was observed, suggesting that the two drugs have different elimination pathways [477523].

Toxicity

GI side effects of licofelone versus indomethacin and diclofenac were examined in a rat and rabbit model, respectively [171427], [198442]. A single oral administration of licofelone (10 to 100 mg/kg) produced no acute GI damage in rats. Repeated oral administration of licofelone at the same doses produced slight, but not significant, GI damage after 5 days, although duodenal ulcers did appear in some rats at doses of 30 and 100 mg/kg, after 11 days. In rabbits, repeated oral administration of licofelone over 4 days did not produce any detectable GI damage at doses of 10 or 30 mg/kg, but an ulcer was observed in one of five rabbits given the 100-mg/kg dose. GI damage from indomethacin (0.3, 1.0 or 3.0 mg/kg) or diclofenac (1.0 or 3.0 mg/kg), however, was more severe and occurred even after a single administration at low doses. The favorable GI tolerability of licofelone is believed to be linked to the mechanism of combined 5-LOX and COX inhibition; LTB_4 levels in the rat stomach were higher in indomethacin- (0.3, 1.0 or 3.0 mg/kg) or diclofenac- (1.0 or 3.0 mg/kg) treated animals (LTB_4 increased by up to 9.2 or 8.9 pg/mg protein over control) than licofelone (10, 30 or 100 mg/kg), which was comparable to control (2.5 pg/mg protein) [472600].

General pharmacological studies demonstrated that oral administration of licofelone (30, 100 or 300 mg/kg) did not affect the central nervous system. Licofelone (100 mg/kg id) had no notable effect on the cardiovascular system, respiration or neuromuscular function in experimental animals. A small transient reduction in urine volume was observed after the highest dose, accompanied by decreases in electrolyte excretion at doses of 100 and 300 mg/kg in rats [198441]. Further study demonstrated that licofelone had no genotoxic potential in bacteria and mammalian cells *in vitro* [183587].

Clinical Development

Phase I

Licofelone (200 mg bid for 5 days and a final dose of 200 mg in the morning of day 6) was well tolerated in 18 young and elderly healthy individuals [477522]. GI tolerability of licofelone was studied with endoscopic evaluation of gastric and duodenal mucosa in healthy volunteers. Healthy individuals (n = 121, mean age of 42 years) with normal gastric and duodenal mucosa were treated for 4 weeks with licofelone (200 or 400 mg bid), placebo or naproxen (500 mg bid). Before and after treatment, the mucosa was evaluated with modified Lanza scores (a standard rating scale of the integrity of the GI mucosa) and ulcers were assessed (3 mm or more in diameter). After 4 weeks, the gastric mucosa was normal in 93% of subjects following treatment with 200 mg bid of licofelone, 89% of those who took 400 mg bid, 90% of those treated with placebo and in 37% of those who took naproxen. No ulcers were present in either the licofelone group or the placebo group; however, six ulcers (20%) were observed in the naproxen group [328497], [385041], [477524].

Phase II

Two double-blind, randomized, placebo-controlled, phase II studies carried out to test the efficacy of licofelone demonstrated a clear dose-response relationship in patients with radiographically and clinically confirmed OA of the knee. In the first study, 107 patients were randomized to receive licofelone (100, 200 or 400 mg bid) or placebo for 4 weeks. Doses of 200 and 400 mg bid were effective at relieving symptoms such as pain and stiffness, as determined using the WOMAC index as a global score, and pain, stiffness and disability as subscores. These scores were highly significant compared with placebo. The second study treated 404 patients with licofelone (100, 200 or 400 mg bid), diclofenac (50 mg tid) or placebo for 4 weeks. All three doses of licofelone produced superior effects compared with placebo, with mean percentage decreases in the WOMAC pain subscore of 37 ($p < 0.025$), 40 ($p < 0.018$) and 42% ($p < 0.005$) for the 100-, 200- and 400-mg doses, respectively. Improvements in secondary endpoints (pain, stiffness and disability) were also greater in the licofelone groups than in the placebo group. No significant difference was noted between the licofelone and diclofenac groups. In both studies, treatment with licofelone was well tolerated across the dose range. Patients in the 100- and 200-mg groups experienced fewer adverse events, including fewer GI events, than the 400-mg group, and a comparable number to placebo treatment. The most common adverse events were diarrhea and abdominal pain [385041], [388969].

Phase III

Patients (n = 148) with OA were administered either licofelone (200 mg bid) or naproxen (500 mg bid) for 12 weeks. A response was defined as a 30% improvement over baseline on the WOMAC index. Efficacy was similar in the two groups, with 69% responding in the licofelone group (n = 72) and 68% in the naproxen group (n = 76). Only 14% of licofelone-treated patients, however, reported GI side effects and 1.5% developed gastroduodenal ulcers, compared with 26 and 15%, respectively, of those on naproxen. The most common adverse events were abdominal pain/discomfort, which were evident in 4.2% of patients on licofelone compared with 7.9% of those on naproxen ($p = 0.03$) [477524], [477531].

The long-term safety and efficacy of licofelone (100 or 200 mg bid) was compared with naproxen (500 mg bid) in a 52-week, double-blind study in 710 patients with OA of the knee. Both doses of licofelone demonstrated a similar efficacy to naproxen at week 4, while the efficacy of licofelone improved throughout the 52 weeks of the study. The general and GI tolerability of licofelone were better than naproxen. Licofelone had a lower incidence of hypertension aggravation than naproxen (0.4% in both doses of licofelone versus 3.1% in naproxen, $p = 0.017$). The total incidence of GI ulcers in phase III studies was 0.14% for the 100-mg bid dose of licofelone, 0.39% for the 200-mg bid dose and 2.5% for naproxen [477531].

The incidence of endoscopically diagnosed ulcers in OA patients has been measured in two studies, one in which all patients took low-dose aspirin and the other in which they did not. Patients were then randomized to receive either licofelone (400 mg bid) or naproxen (500 mg bid). In the low-dose aspirin group, incidence of gastroduodenal ulcers during the first 6 weeks was 25.6 and 5.6% in naproxen- and licofelone-treated patients, while the incidence of gastric ulcers was 23 and 2.4%, respectively. Licofelone-treated

patients in both studies had ulcer incident rates similar to placebo-treated patients in comparable published studies without low-dose aspirin [477532].

Side Effects and Contraindications

Licofelone has fewer general and GI side effects compared with conventional NSAIDs. The most common adverse effects were diarrhea and abdominal pain. No increased ulceration was evident when licofelone was co-administered with aspirin [477532].

Current Opinion

Clinical studies have demonstrated that licofelone is effective in the treatment of OA and is comparable to the conventional NSAIDs naproxen and diclofenac. Licofelone is well tolerated and has fewer side effects than naproxen and diclofenac. These results suggest that dual inhibition of COX and 5-LOX may reduce the undesirable GI side effects associated with NSAIDs. Although it has been suggested that the rate of adverse events associated with licofelone may be comparable to selective COX-2 inhibitors with the possibility of less risk of cardiovascular and thromboembolic complications [477531], there is no direct clinical evidence to support this and further trials are needed to test it. In addition, based on pharmacological studies, it has been suggested that licofelone may be a disease-modifying drug; however, this will need to be determined in well-designed trials [468870]. If these claims are proven, licofelone will become a credible alternative to conventional NSAIDs and selective COX-2 inhibitors in the treatment of OA and capture a substantial proportion of the considerable market for OA therapies. Like conventional NSAIDs, dual COX and 5-LOX inhibitors may also decrease the production of physiological 'housekeeping' PGs, and thus induce potential side effects. The renal side effects of licofelone that occurred in general pharmacological studies should be a matter of concern in further clinical studies [198441].

Licensing

Alfa Wassermann SpA/Laboratoire L Lafon SA/Lacer SA

By December 1995, licofelone was being developed by EuroAlliance, a consortium of Alfa Wassermann SpA, Laboratoire L Lafon SA, Lacer SA and the originator Merckle GmbH. However, Lafon left the agreement in 1996 to 'pursue different strategies' [194999], [227131].

Forest Laboratories Inc

In April 2000, Forest Laboratories Inc licensed the drug from Merckle for development and marketing in the US. No financial details were disclosed. In March 2002, Forest terminated its agreement with Merckle for licofelone, commenting that the likelihood of successfully completing the three pivotal studies required for US approval did not justify the company's continued investment [362605], [443377]. However, in April 2002, Merckle reached an agreement with Forest which would allow the continuation of ongoing clinical trials to develop licofelone for the US market. Both parties agreed that Forest would continue managing the ongoing US placebo-controlled efficacy study for licofelone for a reasonable period until Merckle was in a position to take over full legal and logistical responsibility for completion of the study, although Forest would no longer be involved in the development of the drug [447895].

Development history

Licofelone entered phase III trials in March 2000 for the potential treatment of OA in Germany, Belgium, the Netherlands, Spain, the Czech Republic and Poland [361142]. In 1995, licofelone was also in phase II trials for the treatment of RA and associated pain [194999]. In February 1998, Merckle announced that completion of phase II pilot studies in RA patients was due by March 1998, at which point it hoped to extend phase II trials in the two main indications, RA and OA [280077]. However, no development for RA has been reported since that time.

Developer	Country	Status	Indication	Date	Reference
Alfa Wassermann SpA	Italy	Phase III	Osteoarthritis	03-APR-00	361142
Lacer SA	Spain	Phase III	Osteoarthritis	03-APR-00	361142
Merckle GmbH	Germany	Phase III	Osteoarthritis	03-APR-00	361142
Alfa Wassermann SpA	Italy	Phase II	Inflammation	01-JUL-97	250972
Alfa Wassermann SpA	Italy	Phase II	Pain	01-JUL-97	250972
Lacer SA	Spain	Phase II	Inflammation	01-JUL-97	250972
Lacer SA	Spain	Phase II	Pain	01-JUL-97	250972
Merckle GmbH	Germany	Phase II	Inflammation	01-JUL-97	250972
Merckle GmbH	Germany	Phase II	Pain	01-JUL-97	250972
Alfa Wassermann SpA	Italy	No development reported	Rheumatoid arthritis	04-MAR-03	-

Development history (*continued*)

Developer	Country	Status	Indication	Date	Reference
Lacer SA	Spain	No development reported	Rheumatoid arthritis	04-MAR-03	-
Merckle GmbH	Germany	No development reported	Rheumatoid arthritis	04-MAR-03	-
Forest Laboratories Inc	US	Discontinued	Osteoarthritis	14-MAR-02	443377
Laboratoire L Lafon SA	France	Discontinued	Inflammation	01-NOV-96	227131
Laboratoire L Lafon SA	France	Discontinued	Pain	01-NOV-96	227131

Literature classifications

Key references relating to the drug are classified according to a set of standard heading to provide a quick guide to the bibliography. These headings are as follows:

Chemistry: References which discuss synthesis and structure-activity relationships.

Biology: References which disclose aspects of the drug's pharmacology in animal models.

Metabolism: References that discuss metabolism, pharmacokinetics and toxicity.

Clinical: Reports of clinical phase studies in volunteers providing, where available, data on the following: Whether the experiment is placebo-controlled or double- or single-blind; number of patients; dosage.

Chemistry

Study type	Results	Reference
Synthesis.	Licofelone was synthesized from 1-chloro-3-phenyl-2-propyne in an overall yield of 19%. The method features the use of a thermally induced bicyclization of an ω-acetylenic amino ester.	276312
SAR.	Licofelone, containing a 4-chloro substituent, was the most potent and well-balanced dual inhibitor of COX and 5-LOX.	159855

Biology

Study Type	Effect Studied	Experimental Model	Result	Reference
In vivo	Anti-inflammatory.	Carrageenan-induced rat paw edema.	Licofelone had an ED_{50} value of 17 mg/kg po and completely inhibited both PGE_2 and LTB_4 secretion at a single dose (10, 30 or 100 mg/kg). Indomethacin (10 mg/kg) only inhibited PGE_2.	472618
In vivo	Anti-inflammatory.	Rat adjuvant arthritis.	Decreases in secondary lesions of rats treated with licofelone (25 mg/kg) were similar to the decreases noted with indomethacin (1 mg/kg bid).	472618
In vivo	Analgesic.	Mouse phenyl-quinone writhing model.	Licofelone (30 mg/kg) was more effective than aspirin (50 mg/kg).	472618
In vivo	Antipyretic.	Brewer's yeast-induced hyperthermia model in rats.	A significant antipyretic effect was noted with licofelone (10 mg/kg po) that lasted for 3 h; this was comparable to the effect of indomethacin (10 mg/kg po).	472618
In vivo	Anti-asthmatic.	AC-induced bronchoconstriction in guinea pigs.	Licofelone was highly effective and potent (ED_{50} = 0.2 mg/kg iv).	472618
In vivo	Antithrombotic.	Laser-induced thrombus in rats.	Licofelone (10, 30 and 100 mg/kg po) demonstrated significant antithrombotic activity, comparable with that of aspirin (30 and 100 mg/kg po).	472602
In vivo	Disease-modifying.	Osteoarthritic dogs.	Licofelone (2.5 and 5 mg/kg/day for 8 weeks) significantly decreased the size, grade and severity of cartilage lesions in condyles and plateaus, decreased the level of PGE_2 in synovial fluid and LTB_4 production by synovium, and reduced the levels of collagenase 1 in cartilage and IL-1β in synovial membrane.	472608

Metabolism

Study Type	Effect Studied	Model Used	Result	Reference
In vivo	Pharmacokinetics.	Healthy male and female, young (mean age of 30.9 years) and elderly (mean age of 72.1 years) volunteers.	Maximal plasma concentrations were achieved 0.74 to 4 h after dose administration. The rates of systemic elimination were 11.1 ± 7.0 h in young individuals and 8.7 ± 4.7 h in elderly individuals. The mean $t_{1/2}$ (α) value was 15% higher in the elderly population.	477522

Clinical

Effect Studied	Model Used	Result	Reference
Safety and tolerability.	Phase I trial in healthy volunteers (n = 121) with normal gastric and duodenal mucosa.	After 4 weeks, the gastric mucosa was completely normal in 93% of volunteers given licofelone (200 mg bid), 89% given licofelone (400 mg bid), 90% given placebo and 37% given naproxen (500 mg bid).	477524
Efficacy and safety.	Phase II trial in OA patients (n = 107).	Doses of 100, 200 or 400 mg bid of licofelone for 4 weeks demonstrated a significant, superior effect compared with placebo, and a similar effect to diclofenac (50 mg tid). Treatment with licofelone was well tolerated.	385041 388969
Efficacy and safety.	Phase III trial in OA patients (n = 148).	Efficacy was similar for patients given 200 mg of licofelone bid or 500 mg bid naproxen for 12 weeks. Only 14% of licofelone-treated patients reported GI side effects compared with 26% of those treated with naproxen.	477524
Safety and efficacy.	Phase III trial in patients (n = 710) with OA of the knee.	Doses of 100 or 200 mg bid licofelone demonstrated similar efficacy to naproxen 500 mg bid from week 4. The general tolerability and the GI tolerability of licofelone were better than naproxen.	477531

Associated patent

Title Substituted pyrrole compounds and their use as pharmaceuticals.

Assignee Dannhardt G

Publication EP-00397175 14-NOV-90

Priority DE-03915450 11-MAY-89

Inventors Dannhardt G, Steindl L, Lehr M, Laufer S.

Associated references

- of special interest

159855 **(6,7-Diaryldihydropyrrolizin-5-yl)acetic acids, a novel class of potent dual inhibitors of both cyclooxygenase and 5-lipoxygenase.** Laufer SA, Augustin J, Dannhardt G, Kiefer W *J MED CHEM* 1994 **37** 12 1894-1897

171427 **ML-3000 reduces gastric prostaglandin synthesis without causing mucosal injury.** Wallace JL, Carter L, McKnight W, Tries S, Laufer S *EUR J PHARMACOL* 1994 **271** 2-3 525-531
• *Evaluation of the effects of licofelone on the gastric mucosa, including determination of gastric prostaglandin levels and comparison to diclofenac in terms of ulcerogenic potential in a rabbit model of penetrating, chronic antral ulceration.*

183587 **Studies on the *in vitro* and *in vivo* genotoxicity of [2,2-dimethyl-6-(4-chlorophenyl)-7-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-yl]-acetic acid.** Heidemann A, Tries S, Laufer S, Augustin J *ARZNEIMITTELFORSCHUNG* 1995 **45** 4 486-490

194999 **ML 3000 - press release.** EuroAlliance *PRESS RELEASE* 1995 December 13

198441 **General pharmacology of [2,2-dimethyl-6-(4-chlorophenyl)-7-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-yl]-acetic acid in experimental animals.** Algate DR, Augustin J, Atterson PR, Beard DJ, Jobling CM, Laufer S, Munt PL, Tries S *ARZNEIMITTELFORSCHUNG* 1995 **45** 2 159-165

198442 **Gastrointestinal tolerance of [2,2-dimethyl-6-(4-chlorophenyl)-7-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-yl]-acetic acid in rat.** Laufer S, Tries S, Augustin J, Elsasser R, Algate DR, Atterson PR, Munt PL *ARZNEIMITTELFORSCHUNG* 1994 **44** 12 1329-1333
• *A comparison of the gastric irritant effects of licofelone versus indomethacin in the rat. While providing clear evidence of increased gastric safety, a weakness of this paper is that all of the studies were performed in the rat, where NSAID-induced gastric damage tends to be superficial (involvement of mucosa only) and acute (in contrast to NSAID-induced ulcers in humans).*

215072 **Distribution and excretion of [^{14}C]-labelled [2,2-dimethyl-6-(4-chlorophenyl)-7-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-yl] [2'-^{14}C]-acetic acid in rats.** Deigner HP, Freyberg CE, Laufer S *ARZNEIMITTELFORSCHUNG* 1995 **45** 3 272-276
• *A detailed and thorough study of the metabolism and excretion of licofelone in the rat.*

227131 **Euroalliance anti-inflammatory into phase II.** *SCRIP* 1996 **2184** 20

250972 **Alfa Wassermann/Merckle in Normix deal.** *SCRIP* 1997 **2241** 8

276312 **Synthesis of ML-3000, an inhibitor of cyclooxygenase and 5-lipoxygenase.** Cossy J, Belotti D *J ORG CHEM* 1997 **62** 23 7900-7901
• *A report that describes a short and efficient synthesis of licofelone.*

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